UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JEFFREY R. SAMPSON, and PAUL K. WOLBER

Appeal No. 2006-1800
Application No. 09/632,639

ON BRIEF

Before GRIMES, GREEN, and LEBOVITZ, Administrative Patent Judges.

LEBOVITZ, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to methods of synthesizing nucleic acid molecules. The examiner has rejected the claims as anticipated. We have jurisdiction under 35 U.S.C. § 134. We affirm.

Background

The application describes nucleic acid molecules (e.g., DNA) which contain modified nucleotides that have a reduced ability to base pair with their modified complementary nucleotides, but which can still base pair with their complementary naturally-occurring nucleotides. Specification, pages 4-5; page 16, lines 16-18. Single-stranded nucleic acid molecules containing these modified nucleotides have reduced

secondary structure (e.g., hairpins) because internally complementary nucleotides have a reduced ability to form hydrogen bonds with one another. Id., page 4, lines 15-19; Fig. 15; page 15 (description of Figure 15).

The claimed subject matter is directed to methods of enzmatically synthesizing the nucleic acid molecules in which nucleotides, including complementary pairs of modified precursor nucleotides, are contacted with a DNA or RNA polymerase under conditions which are effective to synthesize a nucleic acid molecule. Id., page 18, line 21-page 19, line 15. At least one pair of nucleotide precursors consists of two modified nucleotides, each of which is unable to base pair with its complementary modified nucleotide, but which retains the ability to base pair with its naturally-occurring complement. See claim 1b).

Discussion

1. Claim construction

Claims 1-26 are on appeal. Appellant has argued the claims as a group. Consequently, the claims stand or fall together. We will focus on claim 1, the broadest claim on appeal. Claim 1 reads as follows:

> A method of synthesizing nucleic acid molecules comprising steps of:
> a) providing at least one nucleic acid template;
> b) providing nucleotide precursors that include at least one pair of complementary nucleotide analog precursors that have a reduced ability to form base pairs with each other, wherein each member of said pair can form a base pair with its complementary naturally occurring nucleotide; and
> c) contacting the template and nucleotide precursors with an enzyme characterized by an ability to polymerize the precursors under conditions and for a time sufficient for synthesis of the nucleic acid molecule.

The method recites the conventional steps involved in enzymatic synthesis of a nucleic acid molecule, where a "nucleic acid template" and nucleotides are contacted with "an enzyme characterized by its ability to polymerize" the nucleotides "under conditions and for a time sufficient for synthesis of the nucleic acid molecule."

The nucleotides include "at least one pair of complementary nucleotide analog precursors that have a reduced ability to form base pairs with each other, wherein each member of said pair can form a base pair with its complementary naturally occurring nucleotide." As explained in the specification, the "nucleotide analogs" are modified complementary nucleotides (e.g., A and T, or C and G) which have a reduced ability to form stable hydrogen bonds with one another, but not with the naturally occurring complement. Specification, page 4, lines 20-23; page 10, lines 23-26. The term "complementary" is used with reference to the nitrogen base which is present in the nucleotide. Id., page 9, lines 11-21. The phrase "to form base pairs" is used conventionally through out the specification to indicate that the nucleotides form hydrogen bonds with one another through Watson-Crick pairing. Id., page 9; page 10, lines 5-8. According to the specification, steric hindrance in some cases prevents modified complementary nucleotides from forming hydrogen bonds with each other, but not with their natural complement. Id., page 25, lines 7-13.

Various examples of modified nucleotides are disclosed. Id., pages 5, 8-9, 22-29. The term "precursor" is defined broadly to mean "a nucleotide monomer that can be used to form a nucleic acid polymer." Id., page 12, lines 13-17. A nucleotide triphosphate is described as a preferred precursor. Id., page 12, line 16.

According to the specification, methods "known in the art" can be used to synthesize the nucleic acid molecules with the claimed properties. Id., page 20, line 20-page 22, line 4. These include methods that employ nucleic acid templates (id., page 21, line 2), nucleotide precursors (id., page 21, lines 3-4, "nucleotide triphosphates"), and polymerase (id., page 21, line 3). Useful enzymes for the synthetic methods are disclosed, including DNA polymerases, RNA polymerases, and reverse transcriptases. Id., page 12, lines 25-29; page 19, line 16-page 20, line 19.

The specification also contains several working examples where nucleic acid molecules were synthesized using nucleotide analog precursors. Id., pages 34-39. The "conditions" include, e.g., the presence of salt, buffers, DNA primers, and different combinations of analogs. Id.

In sum, the specification indicates that the claimed steps a) of "providing at least one nucleic acid template" and c) of "contacting the template and nucleotide precursors" with a polymerase enzyme are carried out according to the conventional methods of nucleic acid synthesis, with the exception that a pair of complementary nucleotide analog precursors with special properties are provided for incorporation (claim 1, step b) into the nucleic acid molecule.

2. Anticipation, 35 U.S.C. § 102(e)

The examiner rejected claims 1-26 under 35 U.S.C. § 102(e) as anticipated by Kutyavin[1].

[1] Kutyavin et al. (Kutyavin), U.S. Pat. No. 5,912,340, issued Jun. 15, 1999.

According to the Answer, "Kutyavin teaches methods of synthesizing nucleic acid molecules comprising the incorporation of pairs of nucleotide analog precursors with a reduced ability to form base pairs with each other (e.g. 2-aminodeoxyadenosine 5'-triphosphate, 2-thiodeoxythymidine or cytidine 5'-triphosphate, pyrrolo pyrimidine triphosphate, inosine triphosphate), employing such enzymes well known in art as polymerases, as claimed in the instant invention (see the abstract, col. 2, line 33- col. 9, line 53, esp. text in col. 4; claims 1-20 and col. 5, col. 34, lines 53- 67; col. 18 and 22-23; claims 1-20, 23-25)." Answer, pages 4-5.

The nucleotide analogs utilized by Kutyavin were stated by the examiner to have the same properties as those which are recited in instant claim 1b). Answer, pages 4 and 6. These analogs are used in Kutyavin to synthesize Selective Binding Complementary (SBC) oligonucleotides (ODN) which are complementary to one another, but unable to stably bind together because they incorporate the nucleotide analogs at complementary positions. Kutyavin, column 2, lines 23-27. Enzymatic synthesis of the SBC oligonucleotides is also described. Id., column 14, lines 35-45; column 28, lines 9-47 ("Example 10").

Appellant argued that "no teaching can be found of any method where one must specifically employ a pair of nucleotide analogs, as claimed in the presently claimed methods. Specifically, claim 1 recites 'A method of synthesizing nucleic acid molecules comprising steps of: ... providing nucleotide precursors that include at least one pair of complementary nucleotide analog precursors that have a reduced ability to form base pairs with each ...' Claim 1 (emphasis added)." Brief, page 13, lines 5-10.

Invalidity based on "anticipation" requires that the invention is not in fact new. See, e.g., Hoover Group, Inc. v. Custom Metalcraft, Inc., 66 F.3d 299, 302, 36 USPQ2d 1101, 1103 (Fed. Cir. 1995). An anticipatory reference must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. Crown Operations International, Ltd. v. Solutia Inc., 289 F.3d 1367, 1375, 62 USPQ2d 1917, 1921 (Fed. Cir. 2002); In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it").

After reviewing the record before, we find that every element of the claimed subject matter is described in the Kutyavin patent. As indicated in the Answer, Kutyavin expressly states that "nucleotides may be incorporated either enzymatically or via chemical synthesis" to form SBC oligonucleotides. Kutyavin, column 14, lines 35-45; Answer, page 4. Kutyavin also discloses a process (nick translation) of synthesizing DNA enzymatically by nick-translation using a nucleic acid template (column 28, line 23: "pHPV-16"), DNA polymerase (column 28, line 22), and an adenine nucleotide analog precursor (column 28, line 38). Compare instant claim 1, steps a, b, and c. Nick-translation is described in Appellant's specification as suitable for synthesizing nucleic acid molecules in accordance with the claimed subject matter. Specification, page 20, line 21. Kutyavin's working example involves the use of a single precursor analog, not a pair of complementary nucleotide analog precursors as required by claim 1b). However, on column 34, lines 53-67, a chemical synthesis method for "the preparation

of oligonucleotides containing 2-thiothymidine and 2-aminoadenosine" is described. See, also Table 2, column 24, which shows a pair of oligonucleotides, SBC(V) and SBC(VI) in which "each dA and dT is replaced with the d2amA [2-aminoadenosine] and d2sT [2-thiothymidine], respectively." Kutyavin, column 24, lines 25-26; column 5, lines 58-61; column 7, lines 4-8. The latter nucleotides are complementary nucleotide analogs that are described in Appellant's own application as meeting the requirements of claim 1b). Specification, page 5, line 3; page 25, line 6. By analogy, enzyme synthesis would require the use of a complementary pair of nucleotide analogs in order to produce the matched pair of oligonucleotides described in the Kutyavin patent, and therefore necessarily result in a process having each and every step of the claimed method. Anticipation requires that a process "necessarily and inevitably" occur from the teachings of the prior art reference. See, e.g., Schering Corp. v. Geneva Pharmaceuticals, 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003). We find that the method of instant claim 1 was known in the prior art by virtue of Kutyavin's direction to use enzymatic synthesis to produce matched pairs of oligonucleotides that "do not form substantially stable hydrogen bonded hybrid with one another" (column 1, lines 52-53) coupled with the mentioned disclosure of chemical and nick-translation oligonucleotide synthesis.

Appellant attempted to distinguish their invention from Kutyavin, stating: "In contrast, the currently pending claims recite a method of producing a nucleic acid molecules [sic] that not only have a reduced ability to form stable hydrogen bonded pairs with each other, but also have a reduced ability to form stable hydrogen bonded intramolecular base pair interactions." (Emphasis added.) Brief, page 13, line 25-page

14, line 3. These arguments fall short. The matched pair of oligonucleotides is expressly described by Kutyavin not to "form substantially stable hydrogen bonded hybrids with one another." Kutyavin, Column 1, lines 51-56. We do not see a difference between Kutyavin's matched pair of oligonucleotides and the nucleic acid molecules prepared according to the claimed method. Both are characterized by the decreased ability of the synthetic nucleic molecules to hybridize together.

Appellant's argument has a second part, relating to the formation of hydrogen bonds between the nucleotide residues in a single nucleic acid molecule ("intramolecular bonds"), e.g., a single-stranded DNA. We find that the property of having a reduced ability to form stable intramolecular bonds is an inherent characteristic of a single-stranded oligonucleotide (nucleic acid) that contains nucleotide analogs which cannot pair with one another. Fig. 15 of Appellant's specification illustrates the reduced ability to form an intramolecular hairpin DNA structure when A and T analogs are incorporated into a DNA. This structure would also occur in the oligonucleotides described by Kutyavin. For example, in Tables 1 and 2 (columns 23-24), oligonucleotides are shown in which the complementary pair dG and dC are replaced by nucleotide analogs dI and dP (column 23, lines 30-32), and in which the complementary pair dA and dT are substituted by nucleotides analogs d2amA and d2sT (column 23, lines 25-26). Each of the complementary analogs has an impaired ability to base pair with its modified complement, but not with its naturally-occurring complement. Thus, an oligonucleotide of Kutyavin has the same appearance as HP51 UNA as shown in Fig. 15, where the naturally-occurring base pairs are substituted by analogs unable to form stable hydrogen bonds with one another. Hairpin and other intramolecular structures

would be reduced because of the unavailability of the internal A and T residues for base pairing. Appellant has not articulated why such a structure would not exist in Kutyavin. Thus, both properties described by Appellant as characteristic of nucleic acids produced by the claimed method would also be possessed by the oligonucleotides disclosed in Kutyavin.

Appellant also stated that "both member of a non-hydrogen bond forming nucleotide pair are necessarily present in each nucleic acid molecule produced" (accounting for the reduced failure to form intramolecular bonds), and suggested that Kutyavin's matched pair of oligonucleotides do not have this requirement. Brief, page 14. In other words, Appellant interprets Kutyavin's invention to be a matched set of oligonucleotides which contain only one nucleotide analog, but not its complement. We do not agree. According to Kutyavin: "A sufficient number of the modified SBC nucleotides are incorporated such that complementary positions in both SBC ODNS are modified into a matched pair of SBC ODNs of the present invention so that the pair of the matched set does not form a stable hybrid." Kutyavin, column 4, lines 39-43. In addition, Kutyavin's Tables 1 and 2 show oligonucleotides in which complementary positions in the matching set are occupied by the modified nucleotides, i.e., both members of the pair of complementary nucleotides are present. See Hybrid IV in Table 1, and SBC(V) and SBC(VI) in Table 2.

Appellant focused on a method described in Kutyavin in which the matched set of oligonucleotides is utilized to bind to duplex DNA. "The disclosure of Kutyavin et al. addresses the specific problem of facilitating strand invasion of a duplex nucleic acid molecule." Brief, page 13, lines 15-17. In explaining this method in the Reply Brief,

Appellant writes: "Kutyavin discloses a matched set of oligonucleotides containing modified nucleotides, where each member of the set is able to hybridize with a complementary strand in a duplex nucleic acid molecule, but is unable to hybridize with the other member of the matched set." Reply Brief, page 4. We do not see the relevance of this argument to the claimed subject matter. Duplex strand invasion (Exhibit A, Scheme A) was not cited in the Answer as pertinent to the anticipation rejection. Kutyavin describes the same method which is recited in claim 1, and which produces oligonucleotide probes having the same properties of the nucleic acid molecules which are a product of the claimed method. Kutyavin also discloses the use of the probes in various methods. This use is independent of the synthetic methods. Scheme A (duplex invasion) is nothing more than a method of using the Kutyavin probes.

In conclusion, we affirm the examiner's rejection of the claims as anticipated. All the claims fall together since Appellant did not provide arguments separately addressing their patentability.

Summary

The rejection of claims 1-26 under 35 U.S.C. § 102(e) is affirmed

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Eric Grimes)
Administrative Patent Judge)
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)
) BOARD OF PATENT
Lora M. Green)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
)
Richard M. Lebovitz)
Administrative Patent Judge)

RML/jlb

Agilent Technologies
Legal Department 51UPD
Intellectual Property Administration
P.O. Box 58043
Santa Clara, CA 95052-8043